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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/664,610	09/16/2003	Charles Wilson	23239-538 (ARC-38)	5499

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EXAMINER
HUMPHREY, LOUISE WANG ZHIYING

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
02/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,610	WILSON ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-66 and 69-126* is/are pending in the application.

4a) Of the above claim(s) *42-45,58,59 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-57,60-64,66 and 69-126* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12 November 2007 has been entered.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

DETAILED ACTION

Claims 1-41, 67 and 68 have been cancelled. Claims 71-126 have been added.

Claims 42-66 and 69-126 are pending. Claims 42-45, 58, 59 and 65 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 46-57, 60-64, 66 and 69-126 are currently examined.

Claim Objections

Claim 114 is objected to because of the following informalities: the hyphen between the words "target" and "wherein" in the first line should be replaced by a comma. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 46-57, 60-64, 66, 69 and 70 under 35 U.S.C. §112, second paragraph, as being indefinite is withdrawn in light of Applicants' rebuttal that the term "target partner" is clearly defined in the specification in paragraph [0072] on page 17.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 46-57, 60-64, 66, 69 and 70 under 35 U.S.C. §103(a) as being obvious over Griffin *et al.* (US 5,756,291) is **maintained and extended** to new claims 71-126.

The instant invention is a method of identifying an aptamer that binds to a target, wherein the binding of the aptamer to the target increases the binding affinity of the target for a target partner, comprising

a) contacting a mixture of nucleic acids with a target partner (TP) or target partner analog (TPA) or both;

b) partitioning the bound nucleic acids from the unbound nucleic acids and retaining the unbound nucleic acids;

c) contacting the unbound nucleic acids with the target and the TP or TPA or both;

d) partitioning bound nucleic acids from unbound nucleic acids; and

e) retaining the bound nucleic acids.

Griffin *et al.* describe a method for identifying aptamers that specifically bind target molecules such as cell surface molecules or glycoproteins (Abstract and col. 13, lines 40-47). Generally, Griffin *et al.* describe various methods (col. 42-80) to identify

aptamer sequences by incubating a pool of oligonucleotides with support-bound target molecules and detaching the resulting target-oligonucleotide complexes from the support. See col. 1, lines 32-59. Specifically, Griffin *et al.* describe a preferred variation, for selection of aptamers that bind to surface antigens, involving a procedure wherein negative selection is first carried out followed by a positive selection. The oligonucleotides are allowed to remain in contact with cell cultures for a sufficient period of time to allow binding between oligonucleotides and cell surfaces which lack the target molecule. When this binding occurs, a negative selection process has been carried out, *i.e.*, nonspecific aptamers can be eliminated by their binding to non-target surfaces. Following this negative selection, a positive selection step is carried out. This is done by combining the oligonucleotides which did not bind to the non-target molecules thereon with a cell culture containing the target molecule on their surface. Such a negative-positive selection protocol can be carried out in a medium containing human or bovine serum in order to select aptamers under simulated physiological conditions. See the paragraph bridging columns 29-30. The bound aptamer population is recovered and amplified as usual. See col. 29, lines 17-27. Griffin *et al.* also disclose that glycoproteins, proteins, carbohydrates, membrane structures, receptors, organelles, and the like can be used as the complexation targets. See column 13, lines 25-27. Most relevantly, Griffin *et al.* an approach wherein a pool of oligonucleotides is subjected to two rounds of selection. The first round involves selecting oligonucleotides that bind to thrombin. The second round involves selecting those oligonucleotides that also bind to a complex between a target (thrombomodulin) and a target partner

(thrombin). See col. 24, lines 1-13. Griffin *et al.* further disclose eluting the bound aptamers with an agonist competitor such as fibrinogen immobilized on a column (column 23, lines 49-51) for further negative selection. The pool of nucleic acids are immobilized on beads (column 23, line 54).

Although Griffin *et al.* do not disclose *ipsis verbis* the specific method steps as claimed, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thrombin/thrombomodulin complex aptamers selection method by the negative-positive aptamer selection suggested by Griffin *et al.*, so that only the unbound oligonucleotides from the first round is used in the second round of selection and the thrombin/thrombomodulin complex-bound oligonucleotides are retained. The skilled artisan would have been motivated to do so to develop complex-favoring aptamers that function as an agonist that delivers the therapeutic ligand to the specific desired receptor and enhance the binding between the ligand and the receptor. There would have been a reasonable expectation of success, given the general protocol of aptamer negative-positive selection protocol with suggested variations to obtained desired aptamers and the teaching that a wide variety of materials, including cell surface glycoproteins, can serve as targets, as taught by Griffin *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that the Griffin patent is solely directed to identifying aptamers that bind to the target regardless of whether or not it is complexed with another molecule and the modification of the negative-positive selection does not remotely

suggest that the resulting aptamers would possess agonist activity. There is no disclosure or discussion of aptamers that bind to and induce a change in the bound target of interest. However, this argument mischaracterizes the rejection because the citation of the negative-positive selection scheme is the suggestion for modifying the positive-positive thrombin-thrombomodulin aptamers selection method into a method as recited in claim 46 because Griffin *et al.* suggest negative selection of aptamers that are directed away from undesired target such as thombomodulin (TP). Furthermore, the selection of thombin-bound nucleotides that also bind to a complex between thrombin and thrombomodulin is the same as the method steps recited in claim 47. The first round of selection of oligonucleotides that bind to thrombin renders the target-based pool of nucleic acid molecules having high affinity and specificity for the target as recited in claims 102 and 112.

The Griffin patent discloses an aptamers selection method that can be modified according to any specific property a skilled artisan desires in the aptamers. Even though the Griffin patent does not express the agonist activity or the property of increasing binding affinity in the aptamers, this advantage would be recognized after the disclosed selection method during the evaluation of the final product. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Applicants' contention that the Griffin aptamers have different functional characteristics than the aptamers in the claimed invention is not persuasive since Griffin

et al. not only disclose the same method steps or similar steps with an obvious variation, but also disclose an allosteric change in the active site conformation of thrombin and an overlap of the thrombomodulin and fibrinogen binding sites on thrombin. Applicants need to provide objective evidence showing that one skilled in the art would not obtain agonistic aptamers if the Griffin method is followed.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
01 February 2008

Louise Humphrey, Ph.D.
Assistant Examiner